REMARKS

Applicants respectfully request reconsideration of the Office Action mailed on May 6, 2008 and allowance of the claims.

The rejection states instant claims 15, 18, 20-22 and 27 are presently under examination. Claims 28-29 are withdrawn from consideration pursuant to 37 C.F.R. 1.142(b) as being directed to non-elected subject matter.

As an initial note Applicants have assumed that claims 15, 18, 20-22 were recombined/restated by the Examiner subsequent to Applicants' February 12, 2008 response. Applicants seek clarification of this issue. Applicants trust that the notations next to each of these claims e.g., "previously presented" are correct in light of the Examiner's restatement of these claims status. In addition, Applicants note the withdrawal of newly added claims 28 and 29 yet claims 15 and 18 which encompass claims 28 and 29 are maintained in the case. Applicants request clarification of this matter.

Claim 22 is objected to for referring to "A combination according to claim 21", which is in error, since claim 21 is directed to a "pharmaceutical composition", not a combination. The objection states Applicant may wish to consider amending the claim to now read ---A composition ~~combination~~ according to claim 21--- to obviate this objection. The objection states Applicant is notified that the adoption of such a suggestion does not necessarily equate to the obviation of any other objection and/or rejection set forth herein.

Applicants have herein amended claim 22 in accordance with the Examiner's suggestion.

Claims 15, 18, 20-22 and 27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (compound of claim 18 and 27 and encompassed by the generic formula of claim 15), does not reasonably provide enablement for the use of the same. The rejection states that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The rejection states in this regard, the application and disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ 2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1. the nature of the invention;
2. the breadth of the claims;
3. the predictability or unpredictability of the art;
4. the amount of direction or guidance presented;
5. the presence or absence of working examples;
6. the quantity of experimentation necessary;

7. the state of the prior art; and

8. the relative skill of those skilled in the art.

The rejection states that the relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The rejection states that the presently claimed invention is directed to a compound of formula (Ib) (instant claim 15), specifically, the elected compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid (instant claims 18 and 27), and a pharmaceutical composition thereof that further comprises one or more pharmaceutically acceptable excipients, diluents or carriers (instant claim 20). The rejection states that the present claims further provide for a pharmaceutical composition comprising a compound of formula (Ib) (i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid) or a pharmaceutically acceptable salt thereof and at least one other therapeutically active agent is a PDEV inhibitor selected from sildenafil, verdenafil, taladafil, etc.

The rejection states that the instant claims are directed to the compound (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as the inclusion of such a compound into a pharmaceutical composition, along with one or more pharmaceutically acceptable excipients, diluents or carries, into which may further be incorporated at least one other therapeutically active agent, such as a PDEV inhibitor, to be used for the treatment of various conditions including epilepsy, faintness attaches, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, functional bowel disorders (e.g., imflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrheal, pelvic pain, cystitis and pancreatisis (p.7, Specification), which are conditions in which the alpha-2-delta receptor "is implicated" (p.9, Specification). The rejection states that however, the instant specification as originally filed lacks adequate guidance, direction or discussion to apprise the skilled artisan how the claimed compound may be used to achieve the disclosed utilities for treating conditions wherein the alpha-2-delta receptor has been implicated, such as epilepsy, faintness attackls, hypokinesia, cranial disorders, neurodegenerative disorders, depression, anxiety, panic, pain, fibromyalgia, sleep disorders, osteoarthritis, rheumatoid arthritis, neuropathological disorders, visceral pain, unctional bowel disorders (e.g., gastroesophageal reflux, dyspepsia, irritable bowel syndrome, functional abdominal pain syndrome, inflammatory bowel diseases, such as Crohn's disease, ileitis, ulcerative colitis) and visceral pain associated with dysmenorrheal, pelvic pain, systitis and pancreatitis (p.7, Specification), with at least a reasonable expectation of successfully achieving the treatment of the same. The rejection states that the instant specification fails to present any evidence, either in the

form of data or scientifically sound reasoning, which would provide such a reasonable expectation that the claimed compounds would have been effective to treat the disclosed disorders. The rejection states that though it is noted that Applicant need not necessarily demonstrate the precise manner in which the claimed therapeutic agent(s) ameliorate a particular disease state, such a mechanism must be elucidated in cases where Applicant relies upon a correlation between the particular activity of a compound (e.g., inhibition of a particular enzyme, binding to a particular receptor, etc.) and a reasonable expectation of efficacy in treating a particular disease.

The rejection states that in the instant case, Applicant relies upon the mechanism of action (i.e., interaction with the alpha-2-delta receptor) underlying the purported biological activity to establish that the genus of the compounds instantly claimed would have been useful for treating conditions in which the alpha-2-delta receptor "is implicated". The rejection states that notably, however, the purported effect and/or specific interaction of the instantly claimed compound with the alpha-2-delta receptor is never described within the four corners of the instant specification. The rejection states that in other words, although Applicant's inventive concept rests upon the correlation between the particular activity of the claimed compounds in interacting with the alpha-2-delta receptor to provide a reasonable expiation of efficacy in treating the disclosed disease(s) or disorder(s), the actual activity of the instantly claimed compound and the receptor with which it is proposed to interact is not adequately described in the accompanying specification so as to enable the full scope of the instant claims.

The rejection states that Applicant provides various compounds and methods of synthesizing each, wherein Example 10 provides a method of synthesizing the instantly claimed compound, (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid, as well as numerous exemplary pharmaceutical formulations that comprise an active ingredient of the claimed compounds of the invention. The rejection states that though Applicant's examples in this regard are duly noted, Applicant has failed to demonstrate that the instantly claimed compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid] actually functions to achieve the disclosed therapeutic use of interacting with the alpha-2-delta receptor such that one of skill in the art would have thereby recognized its efficacious use in treating any one or more of the disclosed disease states. The rejection states that the specification fails to present either view a working or prophetic example(s) or a clear, scientifically sound explanation as to what, in fact, enables the interaction with the alpha-2-delta receptor such that the skilled artisan would have been imbued with at least a reasonable expectation of predictability of action in using the instantly claimed compound for use in treating any one or more of the disorders disclosed as being responsive to such an effect. The rejection states that absent such guidance, the experimentation required to determine if there is any activity

of any of the compounds in treating the disclosed disorders, and further, to determine, without needing to resort to random speculation, what therapeutic amounts would be available to even start testing for a therapeutic effect, would clearly be undue. The rejection states that further, it is noted that, while the lack of a working embodiment cannot be the *sole* factor in determine enablement, the absence of a substantial evidence commensurate in scope with the breadth of the presently claimed subject matter, in light of the unpredictable nature of the chemical and pharmaceutical arts in the limited direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole.

The rejection states that although the instant specification states that the instantly claimed genus of compounds, which encompasses the specifically elected compound [i.e., (2S,4S)-4-(3-fluorobenzyl)-pyrrolidine-2-carboxylic acid], interact in some (unspecified) manner with the alpha-2-delta receptor to treat disorders in which the alpha-2-delta receptor "is implicated", the disclosure fails to provide any mechanisitic discussion or provide any evidence or data, preclinical or otherwise, supporting the concept that the instantly claimed compound would, in fact, be effective to interact in such a way that the alpha-2-delta receptor so as to achieve the therapeutic treatment of the disclosed disorders. The rejection states that in the absence of such discussion or evidence, it is clear that the instant specification fails to support the enablement of the instantly claimed compounds in functioning to interact with the alpha-2-delta receptor such that the skilled artisan would have reasonably expected that the instantly claimed compound, effective in this manner, would have functioned to achieve the disclosed utility for treating conditions in which the alpha-2-delta receptor "is implicated" in a subject in need thereof.

The rejection states that as stated in MPEP §2164.04[R-1], "Doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts in which one skilled in the art could not develop without undue experimentation." The rejection states that in the instant case, the information that is missing is a clear correlation between the claimed compound and its efficacy in treating the disclosed conditions, either through specific evidence in the form of data demonstrating such a fact or at least a sound mechanistic correlation between the claimed compound, *its ability to function in such a manner* and the amenability of the claimed disease state to treatment using an agent capable of functioning in this manner. The rejection states that though one skilled in the art might very well know how to treat a patient with the claimed compound once a diagnosis had been made of the claimed disorder (e.g., epilepsy, hypokinesia, etc.), it remains that the instant specification conspicuously fails to provide any guidance or direction in support of the *reasonable expectation of success* in actually effecting the treatment of the disclosed disorders using the instantly claimed compound in the absence of any evidence

supporting the allegation that the claimed compound is, in fact, effective to achieve such a therapeutic objective, either by reduction to practice or at least by elucidating the mechanism by which the claimed compound works and correlating such activity to therapeutic improvement of the disclosed disorders or diseases. The rejection states that in the absence of this information, the specification fails to provide adequate guidance and/or direction to one of skill in the art at the time of the invention that would have enabled such a person to practice the instantly claimed invention without having to resort to undue experimentation to determine how, in fact, one would achieve the instantly disclosed therapeutic objective(s).

The rejection states that the basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the prior art and Applicant's disclosure and remarks that experimentation in this particular art is not at all uncommon, but that the experimentation required in order to practice the full scope of the invention would be *undue*. The rejection states "please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue.*" (emphasis added)". The rejection states that accordingly, in the absence of any adequate disclosure, direction or guidance as to how one would go about using the instantly claimed compound with a reasonable expectation of successfully treating the disclosed disorder(s), it remains that the pharmaceutical, chemical and medical arts are notoriously complex such that methods of use would have been sufficiently unpredictable to warrant the need for undue experimentation to actually practice the full scope of the invention as instantly claimed.

The rejection states that in view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor or scientist with several years of experience in the art.

The rejection states that as the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation or ability to make and use the full scope of the invention as instantly claimed, given the disclosure and supporting examples provided in the present specification and the state of the art at the time of the invention. The rejection states that in order to actually achieve the claimed invention, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse by the impermissible burden of undue experimentation in order to practice the full scope of the embodiments presently claimed.

Applicants traverse the 35 U.S.C. §112, first paragraph, rejection of the claims and respectfully request that the Examiner withdraw the rejection and allow the claims (as amended).

It is well settled law that the burden is on the Examiner to provide evidence why assertions of utility should not be accepted. In the instant case the Examiner has merely made conclusory statements without any supporting evidence (e.g., publications) why Applicant's assertions of activity should not be accepted as true. Without such supporting information, the rejection of the specification/claims under 35 U.S.C. §112 first paragraph for lack of enablement is contrary to well established law. Ex parte Kenaga, 189 USPQ 61, 64 (P.T.O. Bd. App. 1974), quoting In re Marzocchi, 169 USPQ 367 at 370:

> "It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back assertions of its own with acceptable evidence or reasoning which is in consistent with the contested statement."

The C.C.P.A. held in In re Marzocchi, 169 U.S.P.Q. 367 (C.C.P.A. 1971),

> "[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support."

Id. at 369. The burden is on the Examiner to come forth with evidence to establish a prima facie case. No specific factual evidence (e.g., publications) has been presented to establish a prima facie case pertaining to §112. Therefore, the statements in the present application must be taken as the truth. In re Marzocchi, supra at 369. Thus, Applicants request that the §112 rejection be withdrawn.

This issue has been revisited in In re Brana 34 U.S.P.Q.2d 1437 (CAFC 1995). The court quotes the above quotation from In re Marzocchi and concludes;

> "From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. Id. at 224, 169 U.S.P.Q. at 370. Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility."

In re Brana 34 U.S.P.Q.2d 1437, 1441 (CAFC 1995).

In the instant case the rejection does not provide any evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. In fact, conclusory statements are the only "reasoning" made. This clearly is not sufficient to shift the burden under the standard enunciated by the CAFC.

Applicant submits that in compliance with the above-described case law he has stated that the compounds are effective for their intended use in the specification (e.g., see the instant U.S. published application paragraph [0116]; and paragraphs [0118] through [0131].

Applicant submits that he has fully enabled the use of the instantly claimed compounds. The instant U.S. published application in paragraphs [0207] and [0209], describe appropriate dosage levels. Treatment methods are disclosed in the paragraphs [0172]; [0186]; [0189]; [0196]; [0199]; [0201]; [0205]. Further, the specification teaches (see U.S. published application paragraph [0116]) test protocols which aid in determining the activity/relative activity of the compounds and thus appropriate dosage levels. In addition, the specification is replete with description of how to formulate the compounds. Applicant submits that this is sufficient to meet the standards of enablement under 35 U.S.C. §112.

Finally, Applicants note that the rejection has not stated that the treatment of such diseases is an "incredible utility".

The points and concerns raised by the Examiner having been fully addressed. Applicants urge that this application is in condition for allowance, which action is respectfully requested.

Please charge any additional fees which may be required, or credit any overpayment, to Deposit Account No. 16-1445.

Respectfully submitted,

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